REMARKS

Claim amendments

Claims 7-37, which are drawn to a non-elected invention, have been canceled. Claims 1, 2, 5, 6, 38, 39, 40, 42-44 and 49-51 have been amended. New Claims 56-60 have been added.

As amended, Claims 1, 2, 5, 6 and 38 are directed to a monoclonal antibody having a binding specificity for ouabain, wherein binding of the antibody to ouabain is not inhibited by a concentration of digoxin as high as 100μM (*i.e.,* monoclonal antibodies1-10 and 7-1). Support for the amendment can be found, for example, on page 22, lines 18-20 and Table 1 of the subject specification.

As amended, Claims 40 and 42-44 are directed to a monoclonal antibody having a binding specificity for ouabain, wherein binding of the antibody to ouabain is not inhibited by a concentration of digoxin as high as 25μM (*i.e.,* monoclonal antibody 5A12). Support for the amendment can be found, for example in Table 1 and Figure 3 of the subject specification.

Claim 39 has been amended, and Claims 1, 38, 39, 40 and 44 have been further amended, to indicate that the antibody or antigen binding fragment thereof has binding specificity for the ouabain component of a ouabain-carrier complex. Claims 49-51 have been amended to indicate that the monoclonal antibody or antigen binding fragment thereof has binding specificity for ouabain and for the ouabain component of a ouabain-carrier complex. Support for the amendment can be found, for example, on page 2, lines 18-20; page 9, lines 19-22; page 10, lines 14-15; page 21, lines 18-21; page 22, lines 11-12; page 25, lines 17-21; page 28, lines 1-3 and page 32, lines 5-7.

Newly added Claims 56-60 are directed to a monoclonal antibody having a binding specificity for ouabain and for the ouabain component of a ouabain-carrier complex, wherein binding of the antibody to ouabain is not inhibited by a concentration of digoxin as high as 50μM (*i.e.,* monoclonal antibody 8E4). Support for the amendment can be found, for example, on page 32, lines 5-7 and 15-16 and Figure 6 of the subject specification.

Paragraph 5

Rejection of Claim 2, 5, 6 and 41-43 under 35 U.S.C. §101

Claims 2, 5, 6 and 41-43 remain rejected under 35 U.S.C. §101 "for the reasons previously set forth in Paper No. 14, Section 3, pages 2-3" (Office action, page 3). The Examiner states that as to Claims 2, 5 and 6, the "Declaration is not commensurate in scope with the data presented in the instant application" and that "since no datapoint was presented at 100 micormolar and Awobble@ was found at 70 micromolar, it would be expected that inhibition would only increase from 70 to 100 micromolar" (Office Action, page 3). The Examiner concludes that "the invention appears to be inoperative" (Office Action, page 3).

As used herein, Applicants assume that the Examiner's reference to Paper No. 14 refers to Paper No. 15 and/or Paper No. 12. A Second Declaration of Garner T. Haupert, Jr., M.D. Under 37 C.F.R. §1.132 (the Second Declaration) is being filed concurrently wherein Dr. Haupert states that the concentration of digoxin evaluated in the two-tailed T test and which was discussed in the Declaration of Garner T. Haupert, Jr. M.D. Under 37 C.F.R. §1.132 (the First Declaration), were micromolar (μM), not millimolar (mM), concentrations.

The Examiner further states that as to Claims 41-43, a "review of Figure 3 demonstrates that antibody 5A12 is inhibited by digoxin at less than about 50 micromolar digoxin" and concludes that the "invention appears to be inoperative" (Office Action, pages 3-4).

In the Second Declaration, Dr. Haupert further states that highest μM concentration of digoxin which does not inhibit antibody 5A12 in Figure 3 is 25 μM digoxin. The claims have been amended to clearly indicate that binding of the 5A12 antibody to ouabain is not inhibited by a concentration of digoxin as high as 25μM.

The subject matter of Applicants' claimed invention, particularly as amended, is operative.

Paragraph 6

Rejection of Claims 2, 5, 6 and 41-43 under 35 U.S.C. §112, first paragraph

Claims 2, 5, 6 and 41-43 remain rejected under 35 U.S.C. §112, first paragraph "for the reasons previously set forth in Paper No. 14, Section 5, page 3" (Office Action, page 4). The Examiner further states that "as drawn to claims 41-43, since the embodiments are inoperative

for the reasons set forth above, one of skill in the art would not know how to make and use the claimed invention with a reasonable expectation of success" (Office Action, page 4).

As indicated above, the subject matter of Applicants' claimed invention, particularly as amended, is operative. In the Second Declaration, which is being filed concurrently, Dr. Haupert states that the concentration of digoxin evaluated in the two-tailed T test and which was discussed in the First Declaration, were micromolar (μM), not millimolar (mM), concentrations. In addition, Dr. Haupert states that highest μM concentration of digoxin which does not inhibit antibody 5A12 in Figure 3 is 25 μM digoxin. The claims have been amended to clearly indicate that binding of the 5A12 antibody to ouabain is not inhibited by a concentration of digoxin as high as 25μM.

Applicants have provided an enabling disclosure for the full scope of the claimed invention, particularly as amended.

Paragraph 7

Rejection of Claims 2, 5, 6, 41-43, 45-48 and 53-55 under 35 U.S.C. §112, first paragraph

Claims 2, 5, 6, 41-43, 45-48 and 53-55 remain rejected under 35 U.S.C. §112, first paragraph "for the reasons previously set forth in Paper No. 14, Section 6, pages 3-6" (Office Action, page 4). The Examiner states that "Applicant has not addressed the issue draw[n] to the replacement of the deposit if viable samples cannot be dispensed by the depository as required" (Office Action, page 4).

In the previously filed Reply mailed to the U.S. Patent Office on December 24, 2003, Applicants filed concurrently a Statement Under 37 C.F.R. §1.805(a) (the "Statement") in order to overcome the rejection. In paragraph 2 of the Statement, Applicants' Attorney states that:

> In accordance with 37 C.R.F. §1.805(a), after notification during pendency of the subject application for patent, application for reissue patent or reexamination proceeding that samples of deposit(s) PTA-812, PTA-813, PTA-814 and PTA-815 cannot be furnished or that samples thereof can be furnished but the deposit(s) has become contaminated or has lost its capability to function as described in the specification by the depository, the U.S. Patent and Trademark Office will be notified in writing in each application for patent or patent affected. In addition, a replacement or supplement of the deposit(s) will be made if necessary, which is governed by the same considerations governing the need for making an original deposit under the provisions set forth in 37 C.F.R. §1.802(b).

The Examiner states that the Statement "was not found in the file and appears not to have been submitted" (Office Action, page 2). A copy of the Statement and the postcard receipt date stamped by the U.S. patent Office on December 24, 2003 which indicated that the U.S. Patent Office received the Statement along with the Reply is being filed concurrently.

Accordingly, the rejection has been obviated.

Paragraph 8

Rejection of Claims 1, 3, 4, 39 and 49-51 under 35 U.S.C. §102(b)

Claims 1, 3, 4 and 39 remain rejected under 35 U.S.C. §102(b) "for the reasons previously set forth in Paper No. 14, Section 10, pages 8-10" (Office Action, page 5). The Examiner has not considered Applicants' arguments persuasive "because the claims are drawn to inhibition by digoxin and not to inhibition by BSA or HSA and it is clear that the plasma digoxin did not inhibit binding of the antibody to ouabain, thus the limitations drawn to digoxin inhibition are met absent evidence to the contrary that the claimed product is different from that taught by the prior art and to establish patentable differences" (Office Action, page 5). As to Claims 49-52, the Examiner states that "the claims are drawn to antibodies which have the same binding specificity as antibody 1-10, 7-1, 8E4, all of which bind ouabain" (Office Action, page 5). The Examiner states that "[a]s previously disclosed, the antibody of Lin et al binds ouabain" (Office Action, page 5).

Applicants respectfully disagree. Lin *et al.* injected Balb/C mice with a ouabain-BSA conjugate (Oua-BSA) and spleens cells from mice showing the "***highest titer against ouabain-BSA*** were selected for fusion" (Lin *et al.*, page 131, column 2, emphasis added). Clearly, Lin *et al.* disclose a monoclonal antibody or antigen binding fragment thereof having binding specificity for ouabain-BSA, not ***binding specificity for ouabain***.

Applicants' claimed invention is directed to a monoclonal antibody or antigen binding fragment thereof having binding specificity for ouabain. In the specification as filed, Applicants overcame "the problems associated with protein carrier immunogenicity" by coupling Oua "to the anti-digoxin 26-10 mAb which was derived from A/J mice (Mudgett-Hunter, M., *et al., J.*

Immunol., 129:1165-1171 (1982)) and then hyperimmunized A/J mice with the Oua-26-10 Ab conjugate" (specification, page 21, lines 18-22).

Nevertheless, in order to expedite prosecution, the claims have been amended to indicate that the monoclonal antibody or antigen binding fragment thereof has binding specificity for ouabain and for the ouabain component of a ouabain-carrier complex.

Lin *et al.* do not teach Applicants's claimed invention, particularly as amended.

Paragraph 9

Rejection of Claims 1, 3, 4, 38, 39 and 44 under 35 U.S.C. §103

Claims 1, 3, 4, 38, 39 and 44 remain rejected under 35 U.S.C. §103 "for the reasons previously set forth in Paper No. 14, Section 12, pages 11-13" (Office Action, page 5). The Examiner states that "binding specificity of an antibody of an antibody resides in epitope selectivity" and "it is clear that the antibody of the combined references binds to an epitope on ouabain and therefore has binding specificity for ouabain" (Office Action, page 6).

Applicants respectfully disagree. As indicated in the Reply mailed to the U.S. Patent Office on December 24, 2003, the combined teaching of Blaustein *et al.*, Lin *et al.* and Blaustein would direct one of skill in the art to generate a monoclonal antibody having binding specificity for the ouabain-carrier conjugate used as an immunogen.

In order to expedite prosecution, the claims have been amended to indicate that the monoclonal antibody or antigen binding fragment thereof does not bind to a ouabain-hapten complex. The combined teaching of Blaustein *et al.*, Lin *et al.* and Blaustein do not render obvious Applicants' claimed invention, particularly as amended.

Paragraph 10

Objection to Claims

The Examiner state that "should claim 38 be found allowable, claim 44 will be rejected under 35 U.S.C. 101 as being a substantial duplicate thereof" (Office Action, page 6).

As amended, Claim 44 is drawn to a pharmaceutical composition comprising a monoclonal antibody or antigen binding and an antigen binding fragment thereof fragment thereof having binding specificity for ouabain, wherein binding of the antibody or antigen

binding fragment to ouabain is not inhibited by a concentration of digoxin as high as 25μM, and a pharmaceutical acceptable carrier.

Accordingly, the objection has been obviated.

Paragraph 11

Rejection of claims 1, 3, 4, 38, 39 and 44 under 35 U.S.C. §112, first paragraph

Claims 1, 3, 4, 38, 39 and 44 remain rejected under 35 U.S.C. §112, first paragraph. The Examiner states that the "written description in this case sets forth antibody species, 1-10, 5A12, 7-1, 8E4 and therefore the written description is not commensurate in scope with the claims drawn to antibodies that bind to ouabain but do not crossreact with digoxin" (Office Action, page 7). The Examiner states that "it appears that the instant disclosure does not describe a single monoclonal antibody that binds to ouabain which is not inhibited by 100 micromolar digoxin" (Office Action, page 8).

Applicants respectfully disagree. As indicated above, in the Second Declaration, which is being filed concurrently, Dr. Haupert states that the concentration of digoxin evaluated in the two-tailed T test and which was discussed in the First Declaration, were micromolar (μM), not millimolar (mM), concentrations. In addition, Dr. Haupert states that highest μM concentration of digoxin which does not inhibit antibody 5A12 in Figure 3 is 25 μM digoxin.

In the specification as filed, Applicants clearly describe two monoclonal antibodies having a binding specificity for ouabain, wherein binding of the antibody to ouabain is not inhibited by a concentration of digoxin as high as 100μM (*i.e.*, 1-10 and 7-1). Accordingly, Applicants have met the requirements for written description of the claimed invention.

Paragraph 12

Rejection of Claims 1-4, 6, 38 and 40-44 under 35 U.S.C. §112, first paragraph

Claims 1-4, 6, 38 and 40-44 remain rejected under 35 U.S.C. §112, first paragraph. The Examiner states that the limitation of about 100 micromolar and about 50 micromolar "has no clear support in the specification and the claims as originally filed" (Office Action, page 8). The Examiner states that "a review of the cited support reveals support for the antibody 5A12, 7-1, 1-10 not being inhibited with concentrations" as high as 100 micromolar and that "further, there is

no mention of Antibody 8E4 not being inhibited by concentrations" as high as 100 micromolar (Office Action, page 8). Finally, it is the Examiner's opinion that "a review of the cited support reveals no limitation in the cited claims for" about 50 micromolar and "nothing in Figure 3 that points specifically to the newly claimed limitation" (Office Action, page 8).

As amended, Claims 1-4, 6 and 38 are directed to a monoclonal antibody having a binding specificity for ouabain, wherein binding of the antibody to ouabain is not inhibited by a concentration of digoxin ***as high as 100μM*** (*i.e.,* monoclonal antibodies1-10 and 7-1) which is fully supported on page 22, lines 18-20 and Table 1 of the subject specification. As amended, Claims 40-44 are directed to a monoclonal antibody having a binding specificity for ouabain, wherein binding of the antibody to ouabain is not inhibited by a concentration of digoxin ***as high as 25μM*** (*i.e.,* monoclonal antibody 5A12) which is fully supported in Table 1 and Figure 3 of the subject specification. Newly added Claims 56-60 are directed to a monoclonal antibody having a binding specificity for ouabain, wherein binding of the antibody to ouabain is not inhibited by a concentration of digoxin ***as high as 50μM*** (*i.e.,* monoclonal antibody 8E4) which is fully supported on page 32, lines 15-16 and Figure 6 of the subject specification.

Request for Change of Docket Number

Applicants direct the Examiner's attention to the Request for Change of Docket Number being filed concurrently.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

By Anne J Collins

Anne J. Collins
Registration No. 40,564
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Concord, MA 01742-9133
Dated: April 7, 2005

COPY

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AJC:jcc
December 23, 2003

PATENT APPLICATION
Attorney's Docket No.:0838.1004-000 (MGH-1526)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Behnaz Parhami-Seren, Michael N. Margolies, and Garner T. Haupert, Jr.		
Application No.:	09/412,268	Group:	1642
Filed:	October 5, 1999	Examiner:	Susan NMN Ungar
Confirmation No.:	9455		
For:	Ouabain-Specific Monoclonal Antibodies		

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as First Class Mail in an envelope addressed to Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450

on 12-24-03 Jane Morgan
Date Signature

JANE MORGAN
Typed or printed name of person signing certificate

STATEMENTS UNDER 37 C.F.R. § 1.805(a)

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Pursuant to 37 C.F.R. § 1.805(a) the undersigned states:

1. The above-referenced application, as amended, contains reference to a biological deposit. B cell hybridomas which express anti-ouabain monoclonal antibodies have been created. Specifically, deposits of B cell hybridomas which express 5A12, 7-1, 1-10 and 8E4 anti-ouabain monoclonal antibodies have been made under the terms of the Budapest Treaty on behalf of Massachusetts General Hospital, Building 149, 13th Street, Charlestown, MA 02129-2000 at the American Type Culture Collection (ATCC), 10801 University Boulevard, Manassas, Virginia 20110-2209 under Accession Numbers PTA-812, PTA-813, PTA-814 and PTA-815, respectively.

2. In accordance with 37 C.R.F. §1.805(a), after notification during pendency of the subject application for patent, application for reissue patent or reexamination proceeding that samples of deposit(s) PTA-812, PTA-813, PTA-814 and PTA-815 cannot be furnished or that samples thereof can be furnished but the deposit(s) has become contaminated or has lost its capability to function as described in the specification by the depository, the U.S. Patent and Trademark Office will be notified in writing in each application for patent or patent affected. In addition, a replacement or supplement of the deposit(s) will be made if necessary, which is governed by the same considerations governing the need for making an original deposit under the provisions set forth in 37 C.F.R. §1.802(b).

3. The undersigned is an agent of record.

Respectfully submitted,

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

By Anne J. Collins

Anne J. Collins
Registration No.: 40,564
Telephone (978) 341-0036
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Concord, Massachusetts 01742-9133
Dated: December 24, 2003

COPY

AJC:jcc Docket No.: 0838.1004-000 (MGH-1526) Date: December 24, 2003

This is to acknowledge receipt of the following documents each filed under Certificate of Mailing Procedure 37 C.F.R. 1.8:

__X__ Request for Continued Examination (RCE) Transmittal w/copy
__X__ REPLY __X__ Trans. Fee Ltr. w/copy
____ Affidavit/Declaration ____ documents
____ IDS w/PTO-1449 ____ (pgs.) ____ w/cited refs.
__X__ Petition for Extension of Time w/copy (4 month)
__X__ Check $1,125.00 ____ Authorization to Charge all Fees
__X__ Other Statements Under 37 C.F.R. §1.805(a)

Applicant: Behnaz Parhami-Seren, *et al.*
Application No.: 09/412,268 Filed: October 5, 1999
Title: Ouabain-Specific Monoclonal Antibodies

Date received by the PTO:
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Behnaz Parhami-Seren, Michael N. Margolies, and Garner T. Haupert, Jr.

Application No.: 09/412,268 Group: 1642

Filed: October 5, 1999 Examiner: Ungar, Susan NMN

Confirmation No.: 9455

For: Ouabain-Specific Monoclonal Antibodies

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Apr. 7, 2005 Jenine Crump
Date Signature
Jenine Crump
Typed or printed name of person signing certificate

SECOND DECLARATION OF GARNER T. HAUPERT, JR., M.D. UNDER 37 C.F.R.§1.132

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Garner T. Haupert, Jr., of 512 Great Road, Littleton, Massachusetts, 01460, United States of America, declare and state that:

1. I am an Associate Physician at the Massachusetts General Hospital, and an Assistant Professor of Medicine at Harvard Medical School.

2. I am a co-inventor of the invention claimed in the above-referenced patent application.

3. I have studied the contents of U.S. Application No. 09/412,268 filed October 5, 1999. I have also studied the Office Action mailed from the U.S. Patent and Trademark Office (PTO) on March 3, 2004.

4. In the Office Action, the Examiner states that in the Declaration of Garner T. Haupert, Jr., M.D. Under 37 C.F.R. §1.132 (the First Declaration) which was included in the Reply mailed to the U.S. PTO on October 9, 2002 in the subject application, I declare that "a two-tailed T test of the 70 micromolar point determined that when the inhibitor was digoxin at 50 and 100 mM . . ." (Office Action, page 3). The Examiner notes that the data presented in the subject application is "drawn to 70 micromolar, not millimolar, thus the Declaration is not commensurate in scope with the claimed invention" (Office Action, page 3). The Examiner further states that "Figure 3 demonstrates that antibody 5A12 is inhibited by digoxin at less than about 50 micromolar digoxin" (Office Action, pages 3-4).

5. This Second Declaration of Garner T. Haupert, Jr., M.D. Under 37 C.F.R. §1.132 (the Second Declaration) is being filed in order to correct a typographical error made in the First Declaration, and to clearly identify the highest dose point in Figure 6 of the subject specification which was discussed in the First Declaration. In addition, this Second Declaration is being filed in order to clearly identify the highest μM concentration of digoxin which does not inhibit binding of monoclonal antibody 5A12 to ouabain in Figure 3 of the subject specification.

6. Specifically, this Second Declaration is being filed to correctly state that 1) that the concentrations of digoxin evaluated in the two-tailed T test referred to in the First Declaration were micromolar (μM), not millimolar (mM), concentrations and to clarify that 2) the highest dose point of Figure 6 referred to in the First Declaration is 50 μM.

7. In paragraph 5 of the First Declaration, I stated that:

> Because of the ambiguity in Figure 6 at the highest concentration of digoxin studied, we consulted the raw data in the laboratory notebook for this set of experiments, and applied a statistical analysis ("two-tailed T test") to determine the probability that the data points just above the zero line are in fact different from zero. At every concentration of digoxin tested, the absorbance value in the presence of that dose of digoxin was compared to the absorbance binding value in the absence of any inhibitor (total baseline binding), and the T test applied to determine statistically significant difference between the two values (First Declaration, paragraph 5, page 3).

The generally accepted "p" value to indicate a statistically significant difference is $p \leq 0.05$. When the inhibitor was digoxin at 50 and 100 μM), the result was $p = 0.16$-0.18. This is well above the $p < 0.05$ level, indicating that the digoxin values clustered at the highest dose point in Figure 6 *(i.e., 50μM)* are in fact not different from zero inhibition.

In paragraph 5 of the First Declaration I further stated that:

> Thus, after statistical validation, the results of the inhibition ELISA experiments represented in Figure 6 confirm the absence of digoxin cross-reactivity for mAb 1-10 found by another, more sensitive measure of Ab specificity, fluorescence quenching (Figure 5). This absence of cross reactivity was also documented by a third method, equilibrium saturation binding (see Parhami-Seren et al., J. Immunol. 1999, 163:4360-4366 (Reference AR in PTO 1449), which is our subsequent publication of the data in the referenced application) (First Declaration, paragraph 5, page 3).

See Table I of the subject application and of Parhami-Seren *et al.* wherein it is indicated that for antibodies 1-10, 7-1 and 5A12, the IC_{50} (μM) was "NI", indicating no inhibition at the highest inhibitory concentration (100 μM), in the presence of digoxin (Parhami-Seren *et al., J. Immunol.,163*:4360-4366 (1999), Reference AR in PTO 1449, Table I, legend).

8. In addition, in the Office Action the Examiner states that "Figure 3 demonstrates that antibody 5A12 is inhibited by digoxin at less than about 50 micromolar digoxin" (Office Action, pages 3-4). As shown in Figure 3 of the subject application, 25μM is the highest μM concentration of digoxin which does not inhibit binding of monoclonal antibody 5A12 to ouabain.

9. I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true. Moreover, these statements were made with the knowledge that willful, false statements and the like made by me are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code and that such willful, false statements may jeopardize the validity of the application or any patent issued thereon.

Garner T. Haupert, Jr., M.D.

April 6, 2005

Date

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Behnaz Parhami-Seren, Michael N. Margolies and Garner T. Haupert, Jr.

Application No.: 09/412,268 Group: 1642

Filed: October 5, 1999 Examiner: Ungar, Susan NMN

Confirmation No.: 9455

For: Ouabain-Specific Monoclonal Antibodies

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April 7, 2005 Janine Crump
Date Signature

Janine Crump
Typed or printed name of person signing certificate

REQUEST FOR CHANGE OF DOCKET NUMBER

AND CORRECTED FILING RECEIPT

Customer Correction Office
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Applicant's attorney requests that the docket number of record for the above-referenced case be changed to **0838.1004-000**. This request is made to better identify this application within our offices.

Please provide a corrected Filing Receipt indicating the new attorney docket number.

Please charge Deposit Account No. 08-0380 for any fees that may be due in this matter. One additional copy of this document is enclosed for accounting purposes.

Respectfully submitted,
HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

By Anne J. Collins

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Concord, MA 01742-9133
Date: April 7, 2005